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(FILE 'HOME' ENTERED AT 11:40:10 ON 28 NOV 2006)

INDEX 'ADISCTI, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, ANTE, AQUALINE, AQUASCI, BIOENG, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CAPLUS, CEABA-VTB, CIN, CONFSCI, CROPB, CROPU, DDFB, DDFU, DGENE, DISSABS, DRUGB, DRUGMONOG2, DRUGU, EMBAL, EMBASE, ...' ENTERED AT 11:40:26 ON 28 NOV 2006  
SEA P-GLYCOPROTEIN

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306 FILE ADISCTI  
116 FILE ADISINSIGHT  
76 FILE ADISNEWS  
95 FILE AGRICOLA  
43 FILE ANABSTR  
2 FILE ANTE  
18 FILE AQUALINE  
60 FILE AQUASCI  
290 FILE BIOENG  
11778 FILE BIOSIS  
200 FILE BIOTECHABS  
200 FILE BIOTECHDS  
2794 FILE BIOTECHNO  
523 FILE CABA  
10753 FILE CAPLUS  
36 FILE CEABA-VTB  
52 FILE CIN  
231 FILE CONFSCI  
23 FILE CROPU  
22862 FILE DDFU  
2419 FILE DGENE  
363 FILE DISSABS  
23399 FILE DRUGU  
136 FILE EMBAL  
8298 FILE EMBASE  
5178 FILE ESBIODASE  
8 FILE FROSTI  
15 FILE FSTA  
765 FILE GENBANK  
7 FILE HEALSAFE  
338 FILE IFIPAT  
54 FILE IMSDRUGNEWS  
53 FILE IMSRESEARCH  
1220 FILE JICST-EPLUS  
2 FILE KOSMET  
1630 FILE LIFESCI  
10890 FILE MEDLINE  
39 FILE NTIS  
32 FILE OCEAN  
5113 FILE PASCAL  
70 FILE PHAR  
34 FILE PHARMAML  
83 FILE PHIN  
428 FILE PROMT  
194 FILE PROUSDDR  
1 FILE RDISCLOSURE  
14602 FILE SCISEARCH  
7 FILE SYNTHLINE  
9957 FILE TOXCENTER  
2675 FILE USPATFULL  
316 FILE USPAT2  
170 FILE VETU  
24 FILE WATER

409 FILE WPIDS  
7 FILE WPIFV  
409 FILE WPINDEX  
L1 QUE P-GLYCOPROTEIN  
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FILE 'DRUGU, SCISEARCH, BIOSIS, MEDLINE, CAPLUS, TOXCENTER, EMBASE,  
ESBIOBASE, PASCAL, BIOTECHNO' ENTERED AT 11:41:44 ON 28 NOV 2006

L2 53763 S L1 AND HUMAN  
L3 14704 S L2 AND MDR1  
L4 1335 S L3 AND (ISOLAT? OR PURIF?)  
L5 559 S L4 AND PY<1997  
L6 176 DUP REM L5 (383 DUPLICATES REMOVED)

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L6 ANSWER 166 OF 176 MEDLINE on STN DUPLICATE 87  
 ACCESSION NUMBER: 90315273 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 2576974  
 TITLE: Modulation of drug resistance in a daunorubicin resistant  
 subline with oligonucleoside methylphosphonates.  
 AUTHOR: Vasanthakumar G; Ahmed N K  
 CORPORATE SOURCE: Molecular Biology Section, Southern Research Institute,  
 Birmingham, AL 35255-5305.  
 CONTRACT NUMBER: SO7 RR05676 (NCRR)  
 SOURCE: Cancer communications, (1989) Vol. 1, No. 4, pp.  
 225-32.  
 Journal code: 8916730. ISSN: 0955-3541.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199008  
 ENTRY DATE: Entered STN: 21 Sep 1990  
 Last Updated on STN: 3 Feb 1997  
 Entered Medline: 23 Aug 1990

AB Human K562 erythroleukemia cells were selected in sequential  
 steps for resistance to daunorubicin (K562/III) and found to be  
 cross-resistant to a number of drugs, including vincristine, dactinomycin,  
 doxorubicin, etoposide, and teniposide. In this paper, we report that the  
 K562/III subline showed amplification of an mdrl gene and its  
 4.5 kb transcript. Our results also show that non-ionic oligonucleoside  
 methylphosphonates, complementary to the initiation codon and 15 bases  
 upstream of the mdrl gene, can completely inhibit the synthesis  
 of P-glycoprotein and partially increase the toxicity  
 of daunorubicin.

L6 ANSWER 167 OF 176 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on  
 STN DUPLICATE 88

ACCESSION NUMBER: 1989:404303 BIOSIS  
 DOCUMENT NUMBER: PREV198988073728; BA88:73728  
 TITLE: P-GLYCOPROTEIN GENE MDR1  
 COMPLEMENTARY DNA FROM HUMAN ADRENAL NORMAL  
 P-GLYCOPROTEIN CARRIES GLYCINE-185 WITH  
 AN ALTERED PATTERN OF MULTIDRUG RESISTANCE.  
 AUTHOR(S): KIOKA N [Reprint author]; TSUBOTA J; KAKEHI Y; KOMANO T;  
 GOTTESMAN M M; PASTAN I; UEDA K  
 CORPORATE SOURCE: LAB BIOCHEM, DEP AGRIC CHEM, KYOTO UNIV, KYOTO 606, JAPAN  
 SOURCE: Biochemical and Biophysical Research Communications, (  
 1989) Vol. 162, No. 1, pp. 224-231.  
 CODEN: BBRCA9. ISSN: 0006-291X.  
 DOCUMENT TYPE: Article  
 FILE SEGMENT: BA  
 LANGUAGE: ENGLISH  
 ENTRY DATE: Entered STN: 1 Sep 1989  
 Last Updated on STN: 1 Sep 1989

AB We isolated a full-length MDR1 cDNA from human  
 adrenal where P-glycoprotein is expressed at high  
 level. The deduced amino acid sequence shows two amino acid differences  
 from the sequence of P-glycoprotein obtained from  
 colchicine-selected multidrug resistant cultured cells. The amino acid  
 substitution Gly→Val at codon 185 in P-  
 glycoprotein from colchicine resistant cells occurred during  
 selection of cells in colchicine. As previously reported, cells  
 transfected with the MDR1 cDNA carrying Val185 acquire increased  
 resistance to colchicine compared to other drugs. The other amino acid  
 substitution Ser→Ala at codon 893 probably reflects genetic  
 polymorphism. The MDR1 gene, the major member of the P  
 -glycoprotein gene family expressed in human adrenal,

is sufficient to confer multidrug-resistance on culture cells.

L6 ANSWER 168 OF 176 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on  
STN DUPLICATE 89

ACCESSION NUMBER: 1988:333122 BIOSIS  
DOCUMENT NUMBER: PREV198886039673; BA86:39673  
TITLE: ATP-DEPENDENT TRANSPORT OF VINBLASTINE IN VESICLES FROM  
HUMAN MULTIDRUG-RESISTANT CELLS.  
AUTHOR(S): HORIO M [Reprint author]; GOTTESMAN M M; PASTAN I  
CORPORATE SOURCE: LAB MOL BIOL, BUILD 37, ROOM 4E16, NATL CANCER INST, NIH,  
BETHESDA, MD 20892, USA  
SOURCE: Proceedings of the National Academy of Sciences of the  
United States of America, (1988) Vol. 85, No. 10,  
pp. 3580-3584.  
CODEN: PNASA6. ISSN: 0027-8424.  
DOCUMENT TYPE: Article  
FILE SEGMENT: BA  
LANGUAGE: ENGLISH  
ENTRY DATE: Entered STN: 21 Jul 1988  
Last Updated on STN: 21 Jul 1988

AB Resistance of human cancer cells to multiple cytotoxic hydrophobic agents (multidrug resistance) is due to overexpression of the "MDR1" gene, whose product is the plasma membrane P-glycoprotein. Plasma membrane vesicles partially purified from multidrug-resistant human KB carcinoma cells, but not from drug-sensitive cells, accumulate [3H]vinblastine in an ATP-dependent manner. This transport is osmotically sensitive, with an apparent  $K_m$  of 38  $\mu M$  for ATP and of  $\approx 2 \mu M$  for vinblastine. The nonhydrolyzable analog adenosine 5'-[ $\beta,\gamma$ -imido]triphosphate does not substitute for ATP but is a competitive inhibitor of ATP for the transport process. Vanadate, an ATPase inhibitor, is a potent noncompetitive inhibitor of transport. These results indicate that hydrolysis of ATP is probably required for active transport of vinblastine. Several other drugs to which multidrug-resistant cell lines are resistant inhibit transport, with relative potencies as follows: vincristine > actinomycin D > daunomycin > colchicine = puromycin. Verapamil and quinidine, which reverse the multidrug-resistance phenotype, are good inhibitors of the transport process. These results confirm that multidrug-resistant cells express an energy-dependent plasma membrane transporter for hydrophobic drugs, and establish a system for the detailed biochemical analysis of this transport process.

L6 ANSWER 169 OF 176 MEDLINE on STN

ACCESSION NUMBER: 89024691 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 2902831  
TITLE: The multidrug-resistance gene MDR1.  
AUTHOR: Ueda K; Komano T  
CORPORATE SOURCE: Dept. of Agricultural Chemistry Kyoto University.  
SOURCE: Gan to kagaku ryoho. Cancer & chemotherapy, (1988 Oct) Vol. 15, No. 10, pp. 2858-62.  
Journal code: 7810034. ISSN: 0385-0684.  
PUB. COUNTRY: Japan  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: Japanese  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 198811  
ENTRY DATE: Entered STN: 8 Mar 1990  
Last Updated on STN: 6 Feb 1995  
Entered Medline: 7 Nov 1988

AB MDR1 gene encodes a membrane glycoprotein (P-glycoprotein) that acts as a energy-dependent pump to transport antitumor drugs out of the cells. P-glycoprotein, 1280 amino acids long, consists of two homologous parts of approximately equal length. The protein has binding sites for ATP, antitumor drugs and

calcium channel blockers. MDR1 gene is expressed tissue-specific in human normal adrenal, kidney, liver and colon. The normal function and transcriptional regulation of this gene are also discussed.

L6 ANSWER 170 OF 176 MEDLINE on STN  
ACCESSION NUMBER: 89138016 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 2906314  
TITLE: Sequence of mdr3 cDNA encoding a human P-glycoprotein.  
AUTHOR: van der Bliek A M; Kooiman P M; Schneider C; Borst P  
CORPORATE SOURCE: The Netherlands Cancer Institute, Department of Molecular Biology, Amsterdam.  
SOURCE: Gene, (1988 Nov 30) Vol. 71, No. 2, pp. 401-11.  
Journal code: 7706761. ISSN: 0378-1119.  
PUB. COUNTRY: Netherlands  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 198904  
ENTRY DATE: Entered STN: 6 Mar 1990  
Last Updated on STN: 3 Feb 1997  
Entered Medline: 4 Apr 1989

AB We have determined the sequence of the human mdr3 gene using cDNA derived from liver RNA. The mdr3 gene codes for a member of a family of membrane proteins, the P-glycoproteins, overproduced in many multi-drug-resistant (MDR) cell lines. Like its relatives, the protein encoded by mdr3 has a deduced Mr of 140,000, which is presumably increased by glycosylation after synthesis. The sequence consists of two similar halves, each with a series of six hydrophobic segments that may form a membrane channel. The halves also possess nucleotide-binding consensus sequences, which presumably act as ATPases and drive drug transport. The presumed ATPase domains are all but identical to those of the human mdr1 gene product [Chen et al., Cell 47 (1986) 381-389]. We attribute this high level of sequence conservation to the repeated gene conversion that is evident from segments in which mdr1 and mdr3 differ only in a few silent mutations. Divergence between P-glycoprotein family members is greatest at the N terminus and in the 60 amino acid linker connecting the two halves. In the putative trans-membrane domains approx. 80% of the amino acids are conserved between the products of mdr1 and mdr3. Although the function of mdr3 is not yet known, its high homology with mdr1 suggests that it also encodes an efflux pump with broad specificity.

L6 ANSWER 171 OF 176 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN  
ACCESSION NUMBER: 1988-20975 DRUGU P  
TITLE: Resistance to Multiple Chemotherapeutic Agents in Human Cancer Cells.  
AUTHOR: Gottesman M M; Pastan I  
LOCATION: Bethesda, Maryland, United States  
SOURCE: Trends Pharmacol.Sci. (9, No. 2, 54-58, 1988) 4 Fig. 35 Ref.  
CODEN: TPHSDY ISSN: 0165-6147  
AVAIL. OF DOC.: Laboratory of Molecular Biology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, U.S.A.  
LANGUAGE: English  
DOCUMENT TYPE: Journal  
FIELD AVAIL.: AB; LA; CT  
FILE SEGMENT: Literature

AB Resistance to multiple chemotherapeutic agents in human cancer cells is reviewed. Selection of cultured cells resistant to colchicine (CC), vincristine (VC), vinblastine (VB), etoposide (EP), teniposide (TP), doxorubicin (DX), daunorubicin (DA), plicamycin and actinomycin D

(AD) allows isolation of cross-mutants resistant to all of these agents and others, which express the cell-surface P-glycoprotein (product of MDR1 gene). This can be labeled with N-(p-azido- (3-125I)salicyl)- N-(beta-aminoethyl)- vindesine (125I NV) and labeling is inhibited by VC, VB and agents that reverse drug resistance (verapamil, VE, diltiazem, DI, quinidine, QU and reserpine). Azidopine binds directly to p-glycoprotein. P-glycoprotein is a major component of an energy-dependent efflux system, which occurs in normal tissues and may transport cytotoxic compounds.

L6 ANSWER 172 OF 176 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on  
STN DUPLICATE 90

ACCESSION NUMBER: 1988:112136 BIOSIS  
DOCUMENT NUMBER: PREV198885057606; BA85:57606  
TITLE: ISOLATION AND SEQUENCE OF THE PROMOTOR REGION OF  
THE HUMAN MULTIDRUG-RESISTANCE P  
GLYCOPROTEIN GENE.  
AUTHOR(S): UEDA K [Reprint author]; PASTAN I; GOTTESMAN M M  
CORPORATE SOURCE: LAB MOLECULAR BIOL, NATL CANCER INST, BETHESDA, MD 20892,  
USA  
SOURCE: Journal of Biological Chemistry, (1987) Vol. 262,  
No. 36, pp. 17432-17436.  
CODEN: JBCHA3. ISSN: 0021-9258.  
DOCUMENT TYPE: Article  
FILE SEGMENT: BA  
LANGUAGE: ENGLISH  
ENTRY DATE: Entered STN: 23 Feb 1988  
Last Updated on STN: 23 Feb 1988

AB Intrinsic and acquired multidrug resistance is an important problem in cancer therapy. Multidrug resistance results from overexpression of the MDR1 gene, which encodes a drug-efflux pump called P-glycoprotein. We have isolated a 1-kilobase genomic fragment containing the major transcription initiation sites for the human MDR1 gene. Ribonuclease protection experiments using this fragment indicate that normal human adrenal, colon, and liver cells, the human hepatoma cell line HepG2, and vinblastine-selected human KB multidrug-resistant cells initiate transcription of the MDR1 gene at the same site within this fragment. The 0.43-kilobase region upstream from the major transcription initiation site linked to the chloramphenicol acetyltransferase gene showed promoter activity in CV-1 monkey kidney cells and in human KB cells. The putative promoter region has a consensus CAAT box and two GC box-like sequences, but no TATA sequence. This identification and isolation of promoter sequences for the MDR1 gene will permit studies on how expression of this gene is regulated in normal human tissues and cancers.

L6 ANSWER 173 OF 176 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on  
STN DUPLICATE 91

ACCESSION NUMBER: 1987:339314 BIOSIS  
DOCUMENT NUMBER: PREV198784048257; BA84:48257  
TITLE: EXPRESSION OF A FULL-LENGTH COMPLEMENTARY DNA FOR THE  
HUMAN MDR1 GENE CONFERS RESISTANCE TO  
COLCHICINE DOXORUBICIN AND VINBLASTINE.  
AUTHOR(S): UEDA K [Reprint author]; CARDARELLI C; GOTTESMAN M M;  
PASTAN I  
CORPORATE SOURCE: LAB MOL BIOL, NATL CANCER INST, NATL INST HEALTH, 9000  
ROCKVILLE PIKE, 27/4E16 BETHESDA, MD 20892, USA  
SOURCE: Proceedings of the National Academy of Sciences of the  
United States of America, (1987) Vol. 84, No. 9,  
pp. 3004-3008.  
CODEN: PNASA6. ISSN: 0027-8424.  
DOCUMENT TYPE: Article

FILE SEGMENT: BA  
LANGUAGE: ENGLISH  
ENTRY DATE: Entered STN: 8 Aug 1987  
Last Updated on STN: 8 Aug 1987

AB Intrinsic and acquired multidrug resistance (MDR) is an important problem in cancer therapy. MDR in human KB carcinoma cells selected for resistance to colchicine, vinblastine, or doxorubicin (former generic name adriamycin) is associated with overexpression of the "MDR1" gene, which encodes P-glycoprotein. We previously have isolated an overlapping set of cDNA clones for the human MDR1 gene from multidrug-resistant KB cells. Here we report the construction of a full-length cDNA for the human MDR1 gene and show that this reconstructed cDNA, when inserted into a retroviral expression vector containing the long terminal repeats of Moloney leukemia virus or Harvey sarcoma virus, functions in mouse NIH 3T3 and human KB cells to confer the complete multidrug-resistance phenotype. These results suggest that the human MDR1 gene may be used as a positive selectable marker to introduce genes into human cells and to transform human cells to multidrug resistance without introducing nonhuman antigens.

L6 ANSWER 174 OF 176 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on  
STN DUPLICATE 92

ACCESSION NUMBER: 1988:156880 BIOSIS  
DOCUMENT NUMBER: PREV198885080533; BA85:80533  
TITLE: DETECTION OF MULTIDRUG RESISTANT MARKERS P  
GLYCOPROTEIN AND MDR1 MESSENGER RNA IN  
HUMAN LEUKEMIA CELLS.  
AUTHOR(S): TSURUO T [Reprint author]; SUGIMOTO Y; HAMADA H; RONINSON  
I; OKUMURA M; ADACHI K; MORISHIMA Y; OHNO R  
CORPORATE SOURCE: CANCER CHEMOTHERAPY CENTER, JAPANESE FOUND CANCER RES,  
KAMI-IKEBUKURO, TOSHIMA, TOKYO 170  
SOURCE: Japanese Journal of Cancer Research, (1987) Vol.  
78, No. 12, pp. 1415-1419.  
CODEN: JJCREP. ISSN: 0910-5050.  
DOCUMENT TYPE: Article  
FILE SEGMENT: BA  
LANGUAGE: ENGLISH  
ENTRY DATE: Entered STN: 22 Mar 1988  
Last Updated on STN: 22 Mar 1988

AB We have examined the expression of P-glycoprotein in clinical leukemic cell samples by using a monoclonal antibody (MRK16) against P-glycoprotein. We found that leukemia cells isolated from 3 out of 6 patients with blast crisis of chronic myelogenous leukemia were reactive to MRK16. These 3 cell lines expressed high levels of mdrl mRNA, which codes for P-glycoprotein. The present result indicates that the clinically refractory state of the tumor may be predicted in part by determining P-glycoprotein expression using the monoclonal antibody against P-glycoprotein, and the mdrl probe.

L6 ANSWER 175 OF 176 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation  
on STN

ACCESSION NUMBER: 1987:107641 SCISEARCH  
THE GENUINE ARTICLE: G1082  
TITLE: THE ISOLATION AND SEQUENCE OF CDNA CLONES FOR  
THE MDR1 (P-GLYCOPROTEIN)  
GENE FROM MULTIDRUG-RESISTANT HUMAN KB  
CARCINOMA-CELLS  
AUTHOR: CLARK D (Reprint); UEDA K; FOJO A; CHEN C J; CHIN J;  
RONINSON I; PASTAN I; GOTTESMAN M  
CORPORATE SOURCE: NCI, BETHESDA, MD 20892; UNIV ILLINOIS, COLL MED, CHICAGO,  
IL 60612

COUNTRY OF AUTHOR: USA  
 SOURCE: JOURNAL OF CELLULAR BIOCHEMISTRY, (1987) Supp.  
 [11A], pp. 22-22.  
 ISSN: 0730-2312.  
 PUBLISHER: WILEY-LISS, DIV JOHN WILEY & SONS INC, 111 RIVER ST,  
 HOBOKEN, NJ 07030 USA.  
 DOCUMENT TYPE: Conference; Journal  
 LANGUAGE: English  
 REFERENCE COUNT: 0  
 ENTRY DATE: Entered STN: 1994  
 Last Updated on STN: 1994

L6 ANSWER 176 OF 176 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 93  
 ACCESSION NUMBER: 87042007 EMBASE  
 DOCUMENT NUMBER: 1987042007  
 TITLE: Internal duplication and homology with bacterial transport proteins in the mdrl (P-glycoprotein) gene from multidrug-resistant human cells.  
 AUTHOR: Chen C.-J.; Chin J.E.; Ueda K.; et al.  
 CORPORATE SOURCE: Center for Genetics, University of Illinois College of Medicine at Chicago, Chicago, IL 60612, United States  
 SOURCE: Cell, (1986) Vol. 47, No. 3, pp. 381-389. .  
 CODEN: CELLB5  
 COUNTRY: United States  
 DOCUMENT TYPE: Journal  
 FILE SEGMENT: 037 Drug Literature Index  
 022 Human Genetics  
 029 Clinical Biochemistry  
 016 Cancer  
 LANGUAGE: English  
 ENTRY DATE: Entered STN: 11 Dec. 1991  
 Last Updated on STN: 11 Dec 1991

AB Resistance of tumor cells to multiple cytotoxic drugs is a major impediment to cancer chemotherapy. Multidrug resistance in human cells is determined by the mdrl gene, encoding a high molecular weight membrane glycoprotein (P-glycoprotein). Complete primary structure of human P-glycoprotein has been determined from the cDNA sequence. The protein, 1280 amino acids long, consists of two homologous parts of approximately equal length. Each half of the protein includes a hydrophobic region with six predicted transmembrane segments and a hydrophilic region. The hydrophilic regions share homology with peripheral membrane components of bacterial active transport systems and include potential nucleotide-binding sites. These results are consistent with a function for P-glycoprotein as an energy-dependent efflux pump responsible for decreased drug accumulation in multidrug-resistant cells.

=> d 16 ibib ab 155-165

L6 ANSWER 155 OF 176 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN DUPLICATE 81  
 ACCESSION NUMBER: 1990:178616 BIOSIS  
 DOCUMENT NUMBER: PREV199089095786; BA89:95786  
 TITLE: MECHANISMS OF MULTIDRUG RESISTANCE IN HL60 CELLS DETECTION OF RESISTANCE-ASSOCIATED PROTEINS WITH ANTIBODIES AGAINST SYNTHETIC PEPTIDES THAT CORRESPOND TO THE DEDUCED SEQUENCE OF P-GLYCOPROTEIN.  
 AUTHOR(S): MARQUARDT D [Reprint author]; MCCRONE S; CENTER M S  
 CORPORATE SOURCE: DIV BIOL, KANSAS STATE UNIV, MANHATTAN, KANSAS 66506, USA  
 SOURCE: Cancer Research, (1990) Vol. 50, No. 5, pp.



1426-1430.

CODEN: CNREA8. ISSN: 0008-5472.

DOCUMENT TYPE: Article  
FILE SEGMENT: BA  
LANGUAGE: ENGLISH  
ENTRY DATE: Entered STN: 10 Apr 1990  
Last Updated on STN: 11 Apr 1990

AB HL60 cells isolated for resistance to Adriamycin are multidrug resistant and defective in the cellular accumulation of drug. These cells do not however overexpress *mdr1* and do not contain detectable levels of P-glycoprotein. In the present study we have prepared antisera against synthetic peptides that correspond to various sequence domains of P-glycoprotein and have examined by Western blot analysis the reactivity of these antisera with proteins contained in membranes of HL60/Adr cells. All antisera are highly reactive with a Mr 180,000 (p180) P-glycoprotein contained in membranes of HL60 cells isolated for resistance to vincristine (HL60/Vinc). In contrast, of 13 antisera tested 12 do not react with any resistance-associated protein in the HL60/Adr isolate. One antiserum (ASP14) is however highly reactive with a Mr 190,000 protein (p190) contained in HL60/Adr membranes. This protein is not detected in drug-sensitive cells. ASP14 also reacts with proteins p195 and p50 contained in a second independent HL60/Adr isolate. Analysis of membrane subfractions shows that p190 is located primarily in the endoplasmic reticulum with only low levels contained in plasma membranes. Additional studies demonstrate that endoplasmic reticulum of HL60/Adr cells contain a major Mr 190,000 protein that is capable of binding the photoaffinity agent 8-azido[ $\alpha$ -32P]ATP. p195 contained in a second HL60/Adr isolate is also labeled with 8-azido[ $\alpha$ -32P]ATP. These results thus demonstrate that antiserum against a specific P-glycoprotein sequence detects a p190 (p195) resistance-associated membrane protein in two independent HL60/Adr isolates. p190 (p195) and P-glycoprotein thus contain a minor sequence homology and based on the specificity of ASP14 this occurs in a region which may be involved in nucleotide binding. Possibly this sequence is common to and essential for the functionality of proteins which contribute to resistance by reducing cellular drug levels.

L6 ANSWER 156 OF 176 MEDLINE on STN

ACCESSION NUMBER: 90343281 MEDLINE

DOCUMENT NUMBER: PubMed ID: 1974410

TITLE: Expression of multiple drug resistance gene, *MDR1*, and *N-myc* oncogene in an Italian population of human neuroblastoma patients.

AUTHOR: Corrias M V; Cornaglia-Ferraris P; Di Martino D; Stenger A M; Lanino E; Boni L; Tonini G P

CORPORATE SOURCE: Pediatric Oncology Research Laboratory, G. Gaslini Children's Hospital, Genova, Italy.

SOURCE: Anticancer research, (1990 Jul-Aug) Vol. 10, No. 4, pp. 897-902.

Journal code: 8102988. ISSN: 0250-7005.

PUB. COUNTRY: Greece

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199009

ENTRY DATE: Entered STN: 12 Oct 1990

Last Updated on STN: 6 Feb 1995

Entered Medline: 11 Sep 1990

AB Thirty-four patients of an Italian population affected by neuroblastoma (NB) were evaluated at diagnosis for multidrug resistance gene (*MDR1*) and *N-myc* oncogene amplification. No patients showed *MDR1* amplification, while extra copies of the *N-myc* gene were

found in 9 out of 34 patients (26%). N-myc amplification was correlated ( $p = 0.008$ ) with a shorter progression-free survival. RNA was purified from fresh tumor biopsies and analysed in 29 NB samples. MDR1 gene expression was found to be increased in 5 out of 29 tumor samples at onset (17%) and in 1 out of 3 at relapse, but none of them expressed both MDR1 and N-myc genes simultaneously. No correlation was found between MDR1 or N-myc genes expression and tumor progression. MDR1 mRNA transcription may occur spontaneously after onset, suggesting that certain NB tumors could be resistant to antineoplastic drugs at onset. All 5 patients showing MDR1 mRNA transcription achieved complete or partial clinical remission after polychemotherapy. This was presumably due to inclusion in the therapeutic protocol of a high dose of Cisplatin, a drug not susceptible to the effects of the MDR1 gene product. Our findings show that cells which actively transcribe for the MDR1 gene are present in several untreated NB patients. No gene amplification was detected and probably the MDR1 gene expression is regulated at the transcriptional level.

L6 ANSWER 157 OF 176 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on  
STN DUPLICATE 82

ACCESSION NUMBER: 1990:416809 BIOSIS  
DOCUMENT NUMBER: PREV199090077610; BA90:77610  
TITLE: MULTIDRUG RESISTANCE IN CELLS TRANSFECTED WITH  
HUMAN GENES ENCODING A VARIANT P  
GLYCOPROTEIN AND GLUTATHIONE S-TRANSFERASE-PI.  
AUTHOR(S): FAIRCHILD C R [Reprint author]; MOSCOW J A; O'BRIEN E E;  
COWAN K H  
CORPORATE SOURCE: BRISTOL-MYERS SQUIBB CO, EXPERIMENTAL THERAPEUTICS/DEP 204,  
PO BOX 5100, 5 RESEARCH PARKWAY, WALLINGFORD, CONN 06492,  
USA  
SOURCE: Molecular Pharmacology, (1990) Vol. 37, No. 6,  
pp. 801-809.  
CODEN: MOPMA3. ISSN: 0026-895X.  
DOCUMENT TYPE: Article  
FILE SEGMENT: BA  
LANGUAGE: ENGLISH  
ENTRY DATE: Entered STN: 17 Sep 1990  
Last Updated on STN: 17 Sep 1990

AB The nucleotide sequence of the *mdr1* gene encoding a putative drug efflux pump (P-glycoprotein) is homologous to a class of bacterial membrane-associated transport proteins. These bacterial proteins are part of a multicomponent system that includes soluble periplasmic proteins that bind substrates, channeling them through the membrane in an energy-dependent manner. We have investigated the possibility that a similar multicomponent transport system exists in a multidrug-resistant human MCF-7 breast cancer cell line that was initially selected for resistance to doxorubicin (AdrR MCF-7). AdrR MCF-7 cells overexpress both the *mdr1* gene and the  $\pi$  class isozyme of glutathione S-transferase (GST- $\pi$ ) (EC 2.5.1.18). The latter is one of several isozymes known to have a ligand-binding function in addition to drug-metabolizing capabilities. Although we have recently shown that transfection of a functional GST- $\pi$  expression vector is insufficient to confer resistance to doxorubicin in cells that lack P-glycoprotein expression [Mol. Pharmacol. 36:22-28 (1989)], we examined the possibility that GST- $\pi$  interacts with P-glycoprotein to alter multidrug resistance. To do this, we have cloned cDNAs encoding these proteins from AdrR MCF-7 cells, constructed expression vectors containing these two genes, and transfected these vectors sequentially into drug-sensitive MCF-7 cells. The human *mcrl* cDNA isolated from AdrR MCF-7 is a variant gene whose sequence differs from that isolated previously from vinblastine-resistant KB cells [Cell 53:519-529 (1989)], resulting in a amino acid substitution of alanine to serine at position 893 (*mdr1*

/893ala). Transfection of eukaryotic expression vectors containing the *mdr1* gene isolated from AdrR MCF-7 cells produced a multidrug-resistant phenotype in recipient cells, with a cross-resistance pattern similar to that in the Adr MCF-7 cells. To determine whether GST- $\pi$  expression could augment resistance provided by *mdr1*, two clones transfected with *mdr1*, one with high levels (153% of *mdr1* RNA in Adr MCF-7 cells) and one with low levels (10% of *mdr1* RNA in AdrR MCF-7 cells), were subsequently cotransfected with a GST- $\pi$  expression vector and pSVNeo and selected for resistance to G418. Six of these clones contained levels of GST- $\pi$  that were 8- to 18-fold greater than GST levels found in *mdr1*-expressing clones transfected with nonspecific DNA. We found no difference in the degree of resistance to doxorubicin, actinomycin D, and vinblastine between the clones expressing *mdr1* only and the clone expressing both *mdr1* and GST- $\pi$ . Therefore, under these conditions, GST- $\pi$  does not appear to act in conjunction with P-glycoprotein to alter the pattern or level of multidrug resistance in MCF-7 cells.

L6 ANSWER 158 OF 176 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN  
 ACCESSION NUMBER: 1990-50848 DRUGU P B  
 TITLE: Intrinsic and Acquired Resistance (R) to Adriamycin (Ad) in Human Colon Carcinoma Cell Lines (HCCCL).  
 AUTHOR: Lai G M; Chen Y N; Mickley L A; Fojo A T; Bates S E  
 LOCATION: Taipei, Taiwan; Bethesda, Maryland, United States  
 SOURCE: Proc.Am.Assoc.Cancer Res. (31, 81 Meet., 380, 1990) ISS  
 N: 0197-016X  
 AVAIL. OF DOC.: Chang-Gung Memorial Hospital, Taipei, Taiwan.  
 LANGUAGE: English  
 DOCUMENT TYPE: Journal  
 FIELD AVAIL.: AB; LA; CT  
 FILE SEGMENT: Literature

AB SW620, LS180, DLD1 and HCT15 HCCCL and sublines isolated in-vitro with Ad (Adriamycin, doxorubicin) were studied for mechanisms of intrinsic and acquired Ad R. In SW620 sublines, there was a correlation between Ad R, levels of *mdr1* mRNA, P-glycoprotein (Pgp), decreasing drug accumulation and reversibility by verapamil (Vp). In LS180, DLD1, HCT15 and their *mdr1* expressing sublines no such correlation was observed. LS180 cells and Ad resistant sublines had less GSH depletion by buthionine sulfoximine (BSO) and enhanced rate of recovery. Acquired R in LS180 Ad resistant cells was reversed by BSO, suggesting a role for the GSH redox cycle. It is concluded that there is a role for drug R modulating agents in colon cancer therapy. (congress abstract).

L6 ANSWER 159 OF 176 CAPLUS COPYRIGHT 2006 ACS on STN  
 ACCESSION NUMBER: 1991:441422 CAPLUS  
 DOCUMENT NUMBER: 115:41422  
 TITLE: Comparative cytotoxicities of a series of ellipticine and olivacine derivatives on multidrug resistant cells of human and murine origins  
 AUTHOR(S): Chevallier-Multon, Marie Christine; Jacquemin-Sablon, Alain; Besselievre, Richard; Husson, Henri Philippe; Le Pecq, Jean Bernard  
 CORPORATE SOURCE: Lab. Pharmacol. Mol., Inst. Gustave-Roussy, Villejuif, 94805, Fr.  
 SOURCE: Anti-Cancer Drug Design (1990), 5(4), 319-35  
 CODEN: ACDDEA; ISSN: 0266-9536  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB The MDR P-glycoprotein has been described as a major factor of multidrug resistance. This transmembrane glycoprotein acts like an energy-dependent efflux pump which possesses a broad specificity. It seems to be acting as a pump requiring drug fixation prior to extrusion.

With the aim of investigating which parameters influence the recognition of drugs by the MDR system, the toxicities of different drugs on human and murine sensitive and resistant cell lines were determined. For this purpose, a human adriamycin-resistant cell line, CEM/Adr, which presents an MDR phenotype was isolated and characterized. The tested drugs were ellipticine and olivacine derivs. which differ through discrete lateral chain substitutions. The influence of lateral chain lipophilicity and nitrogen quaternization on drug recognition was studied. Small modifications in the chemical structure of the drugs have induced large changes in their toxicities and in the cross-resistance levels of the MDR cells to the tested compds. The cross-resistances of the murine and human cells to the various compds. were strikingly different. The validity of murine screening models in the selection of antitumor drugs for human therapy must therefore be questioned.

L6 ANSWER 160 OF 176 MEDLINE on STN . DUPLICATE 83  
 ACCESSION NUMBER: 92202110 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 1983721  
 TITLE: Multidrug resistance: a transport system of antitumor agents and xenobiotics.  
 AUTHOR: Tsuruo T  
 CORPORATE SOURCE: Institute of Applied Microbiology, University of Tokyo, Japan.  
 SOURCE: Princess Takamatsu symposia, (1990) Vol. 21, pp. 241-51. Ref: 42  
 Journal code: 9301172.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 General Review; (REVIEW)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199204  
 ENTRY DATE: Entered STN: 9 May 1992  
 Last Updated on STN: 6 Feb 1995  
 Entered Medline: 28 Apr 1992

AB Resistance of tumors to a variety of chemotherapeutic agents presents a major problem in cancer treatment. Resistance to such agents as doxorubicin, Vinca alkaloids, and actinomycin D can be acquired by tumor cells after treatment with a single drug. The gene responsible for multidrug resistance, termed *mdr1*, encodes a membrane glycoprotein (P-glycoprotein) that acts as a pump to transport various cytotoxic agents including various xenobiotics out of the cell. The amount of P-glycoprotein expression has been measured in tumor samples and was found to be elevated in intrinsically drug-resistant cancers of the colon, kidney, and adrenal as well as in some tumors that acquired drug resistance after chemotherapy. The protein was also found to be elevated in cells treated with xenobiotics. P-glycoprotein has been shown to bind anticancer drugs and several resistance-reversing agents including calcium channel blockers, and to be an ATPase. We recently reconstituted the purified P-glycoprotein into artificial liposomes. Reconstituted P-glycoprotein showed ATPase activity, ATP-dependent drug-transport activity, and calcium channel blocker-binding activity. This model provides many advantages for studies of the biochemical functions of P-glycoprotein. In addition to these basic interests, the protein is of considerable interest as a target for cancer chemotherapy because it appears to be involved in both acquired multidrug resistance and intrinsic drug resistance in human cancer. The selective killing of tumor cells expressing P-glycoprotein could be very important in future cancer therapy.

L6 ANSWER 161 OF 176 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1990:137043 CAPLUS  
DOCUMENT NUMBER: 112:137043  
TITLE: Use of recombinant P-glycoprotein fragments to produce antibodies to the multidrug transporter  
AUTHOR(S): Tanaka, Shigeo; Currier, Stephen J.; Bruggemann, Edward P.; Ueda, Kazumitsu; Germann, Ursula A.; Pastan, Ira; Gottesman, Michael M.  
CORPORATE SOURCE: Lab. Mol. Biol., Natl. Cancer Inst., Bethesda, MD, 20892, USA  
SOURCE: Biochemical and Biophysical Research Communications ( 1990), 166(1), 180-6  
CODEN: BBRCA9; ISSN: 0006-291X  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB Multidrug-resistance of human cancer cells may result from expression of a 170,000 dalton multidrug efflux pump called P-glycoprotein. To identify this multidrug transporter, and to study its structure and function, polyclonal rabbit antibodies were generated against the N-terminal and C-terminal halves of the mol. using recombinant protein fragments produced in Escherichia coli. Two recombinant P-glycoprotein fragments, representing amino acids 140-228 and 919-1280, were overproduced in E. coli by an inducible T7 expression system, gel-purified, and injected into rabbits. Both antisera specifically immunoppt. 3H-azidopine and 35S-methionine labeled P-glycoprotein from multidrug-resistant cells and detect P-glycoprotein on Western blots with high sensitivity. Because these antisera were raised against epitopes in the N- and C-terminal halves of P-glycoprotein, they should be useful as research tools to define the function of these 2 halves of the mol.

L6 ANSWER 162 OF 176 CAPLUS COPYRIGHT 2006 ACS on STN  
ACCESSION NUMBER: 1992:419735 CAPLUS  
DOCUMENT NUMBER: 117:19735  
TITLE: Proteins involved in multidrug resistance and their implication for therapy  
AUTHOR(S): Tsuruo, Takashi  
CORPORATE SOURCE: Cancer Chemother. Cent., Tokyo, Japan  
SOURCE: Drug Resist.: Mech. Reversal, [Int. Annu. Pezcoller Symp.], 1st (1990), Meeting Date 1989, 131-43. Editor(s): Mihich, Enrico. John Libbey CIC: Rome, Italy.  
CODEN: 57STAN  
DOCUMENT TYPE: Conference; General Review  
LANGUAGE: English

AB A review with 15 refs. of purifn. and characterization of P-glycoprotein as a target for new therapeutic approaches, use of monoclonal antibodies for diagnosis and therapy of resistant human tumors. Also discussed are the search for new agents capable of reversing drug resistance, the development of agents effective against resistant cells, and the identification of proteins involved in multidrug resistance by means of monoclonal antibodies.

L6 ANSWER 163 OF 176 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN  
DUPLICATE 84  
ACCESSION NUMBER: 1990:50960 BIOSIS  
DOCUMENT NUMBER: PREV199089028324; BA89:28324  
TITLE: MECHANISMS OF MULTIDRUG RESISTANCE IN HL60 CELLS ANALYSIS OF RESISTANCE ASSOCIATED MEMBRANE PROTEINS AND LEVELS OF MDR GENE EXPRESSION.  
AUTHOR(S): MCGRATH T [Reprint author]; LATOUD C; ARNOLD S T; SAFA A R; FELSTED R L; CENTER M S  
CORPORATE SOURCE: DIV BIOL, KANS STATE UNIV, MANHATTAN, KANS 66506, USA

SOURCE: Biochemical Pharmacology, (1989) Vol. 38, No. 20,  
pp. 3611-3620.  
CODEN: BCPA6. ISSN: 0006-2952.  
DOCUMENT TYPE: Article  
FILE SEGMENT: BA  
LANGUAGE: ENGLISH  
ENTRY DATE: Entered STN: 11 Jan 1990  
Last Updated on STN: 11 Jan 1990

AB HL60 cells isolated for resistance to Adriamycin do not contain P-glycoprotein, as determined with immunological probes. These cells, however, are multidrug resistant and defective in the cellular accumulation of drug. In view of these findings, we have examined in greater detail certain properties of the HL60/Adr cells and have compared these properties to an HL60 drug-resistant isolate (HL60/Vinc) which contains high levels of P-glycoprotein. The results of these studies demonstrated that verapamil induces a major increase in cellular drug accumulation in both HL60/Adr and HL60/Vinc isolates. An 125I-labeled photoaffinity analog of verapamil labeled P-glycoprotein contained in membranes of HL60/Vinc cells. In contrast, this agent did not label any protein selectively associated with drug resistance in membranes of the HL60/Adr isolate. The photoactive dihydropyridine calcium channel blocker [3H]azidopine and [125I]NASV, a photoaffinity analog of vinblastine, labelled P-glycoprotein in membranes from HL60/Vinc cells, whereas in experiments with the HL60/Adr isolate there was no detectable labeling of a drug resistance associated membrane protein. Additional studies have been carried out to analyze membrane proteins of HL60/Adr cells labeled with the photoaffinity agent 8-azido- $\alpha$ -[32P]ATP (AzATP32). The results demonstrate that this agent labeled a resistance associated membrane protein of 190 kilodaltons (P190). P190 is essentially absent in membranes of drug-sensitive cells. Labeling of P190 with AzATP32 in membranes of resistant cells was blocked completely when incubations were carried out in the presence of excess unlabeled ATP. Additional studies were carried out to analyze mdr gene amplification and expression in sensitive and resistant cells. Experiments carried out with human 5',mdr1 (1.1 kb) and mdr3 (1.0 kb) cDNA demonstrate that both of these sequences were highly amplified in the HL60/Vinc isolate. Only the mdr1 gene sequence however, was overexpressed. In contrast, there was no detectable amplification or overexpression of mdr1 or mdr3 sequences in HL60/Adr cells. The results of this study thus identify a new nucleotide binding protein which is overexpressed in membranes of HL60 cells isolated for resistance to Adriamycin. P190, which exhibits properties distinct from P-glycoprotein, possibly functions in the energy-dependent drug efflux system contained in the HL60/Adr resistant isolate.

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STN DUPLICATE 85

ACCESSION NUMBER: 1990:111431 BIOSIS  
DOCUMENT NUMBER: PREV199089060922; BA89:60922  
TITLE: DETECTION OF MULTIDRUG RESISTANCE MDR1 GENE RNA  
EXPRESSION IN HUMAN TUMORS BY A SENSITIVE RNASE  
PROTECTION ASSAY.  
AUTHOR(S): UEDA K [Reprint author]; YAMANO Y; KIOKA N; KAKEHI Y;  
YOSHIDA O; GOTTESMAN M M; PASTAN I; KOMANO T  
CORPORATE SOURCE: LAB BIOCHEM, DEP AGRIC CHEM, KYOTO UNIV, KITASHIRAKAWA,  
SAKYO-KU, KYOTO 606  
SOURCE: Japanese Journal of Cancer Research, (1989) Vol.  
80, No. 11, pp. 1127-1132.  
CODEN: JJCREP. ISSN: 0910-5050.  
DOCUMENT TYPE: Article  
FILE SEGMENT: BA  
LANGUAGE: ENGLISH

ENTRY DATE: Entered STN: 21 Feb 1990  
Last Updated on STN: 22 Feb 1990

AB The human MDR1 gene encoding P-glycoprotein, an energy-dependent drug-efflux pump, was initially isolated from a multidrug-resistant KB carcinoma cell. When a 3 kb genomic sequence isolated from normal human tissue including the major downstream promoter and the first and second exons of the MDR1 gene was compared to the equivalent fragment from KB cells, the MDR1 gene from KB carcinoma cells was found to have a point mutation in the first exon. Although this mutation does not affect the downstream promoter sequence or the coding sequence of the MDR1 gene, it creates a single base mismatch between the 5' KB genomic fragment previously used for RNase protection analysis of MDR1 RNA expression in normal tissues and thereby reduces the sensitivity of this assay. Using the DNA fragment from normal tissues rather than KB cells, we have reanalyzed MDR1 mRNA levels in 12 renal carcinomas and 4 colon adenocarcinomas. By this RNase protection assay, MDR1 RNA levels are as high in these tumors as in the multidrug-resistant cell line, KB-8-5. The ribonuclease protection assay indicated that the major downstream promoter was mainly used in these clinical samples including two samples of RNA from metastatic renal cancer. This assay appears to be a very sensitive and specific assay for detecting MDR1 mRNA levels and mRNA initiation sites in clinical samples.

L6 ANSWER 165 OF 176 MEDLINE on STN DUPLICATE 86  
ACCESSION NUMBER: 89330565 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 2569166  
TITLE: The yeast STE6 gene encodes a homologue of the mammalian multidrug resistance P-glycoprotein.  
AUTHOR: McGrath J P; Varshavsky A  
CORPORATE SOURCE: Department of Biology, Massachusetts Institute of Technology, Cambridge 02139.  
SOURCE: Nature, (1989 Aug 3) Vol. 340, No. 6232, pp. 400-4.  
Journal code: 0410462. ISSN: 0028-0836.  
PUB. COUNTRY: ENGLAND: United Kingdom  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
OTHER SOURCE: GENBANK-X15428  
ENTRY MONTH: 198909  
ENTRY DATE: Entered STN: 9 Mar 1990  
Last Updated on STN: 6 Feb 1995  
Entered Medline: 6 Sep 1989

AB Mammalian tumours displaying multidrug resistance overexpress a plasma membrane protein (P-glycoprotein), which is encoded by the MDR1 gene and apparently functions as an energy-dependent drug efflux pump. Tissue-specific expression of MDR1 and other members of the MDR gene family has been observed in normal cells, suggesting a role for P-glycoproteins in secretion. We have isolated a gene from the yeast *Saccharomyces cerevisiae* that encodes a protein very similar to mammalian P-glycoproteins. Deletion of this gene resulted in sterility of MATa, but not of MAT alpha cells. Subsequent analysis revealed that the yeast P-glycoprotein is the product of the STE6 gene, a locus previously shown to be required in MATa cells for production of a-factor pheromone. Our findings suggest that the STE6 protein functions to export the hydrophobic a-factor lipopeptide in a manner analogous to the efflux of hydrophobic cytotoxic drugs catalysed by the related mammalian P-glycoprotein. Thus, the evolutionarily conserved family of MDR-like genes, including the hlyB gene of *Escherichia coli* and the STE6 gene of *S. cerevisiae*, encodes components of secretory pathways distinct from the classical, signal sequence-dependent protein

translocation system.

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